AMENDMENTS TO THE CLAIMS

1. (Withdrawn) A cell-containing preparation comprising a cell which has a DNA having a base sequence represented by SEQ ID NO: 1 or 2 or a DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 1 or 2 under stringent conditions and a fibrous protein.

2. (Withdrawn) The cell-containing preparation according to claim 1, wherein the cell is an epithelial cell of the oral mucosa, a skin cell or a fibroblast.

3. (Withdrawn) The cell-containing preparation according to claim 1, wherein the fibrous protein is collagen.

4. (Withdrawn) The cell-containing preparation according to claim 1, wherein the cells are deposited on the surface of the fibrous protein.

5. (Withdrawn) The cell-containing preparation according to claim 1, wherein the cell is a transformant.

6. (Withdrawn) The cell-containing preparation according to claim 5, wherein the transformant is transformed with a recombinant expression vector.

7. (Withdrawn) The cell-containing preparation according to claim 6, wherein the recombinant expression vector is adeno-associated virus (AAV), retrovirus, poxvirus, herpes virus, herpes simplex virus, lentivirus (HIV), Sendai virus, Epstein-Barr virus (EBV), vaccinia virus, polio virus, sindbis virus, SV40 or plasmid.

8. (Withdrawn) The cell-containing preparation according to claim 1 capable of forming a peptide encoded by a DNA having a base sequence represented by SEQ ID NO: 1 or 2, or by a DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 1 or 2 under stringent conditions.

9. (Withdrawn) The cell-containing preparation according to claim 1 further containing a mesh sheet comprising a biodegradable resin.

10. (Withdrawn) The cell-containing preparation according to claim 9, wherein the biodegradable resin is polyglycolic acid.

11. (Withdrawn) The cell-containing preparation according to claim 1, which is an anticancer agent or a cancer metastasis inhibitor.

12. (Withdrawn) The cell-containing preparation according to claim 11, which is an anticancer agent or a metastasis inhibitor for ovarian cancer, pancreatic cancer, stomach cancer, gall bladder cancer, kidney cancer, prostate cancer, breast cancer, esophageal cancer, liver cancer, oral cavity cancer, colon cancer, large intestine cancer, sarcoma, glioma or melanoma.

13. (Withdrawn) The cell-containing preparation according to claim 1, which is an angiogenesis inhibitor.

14. (Withdrawn) A method for inhibiting growth, invasion and metastasis of cancers or for inhibiting angiogenesis, which comprises administering a cell-containing preparation comprising a cell which has a DNA having a base sequence represented by SEQ ID NO: 1 or 2 or a DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 1 or 2 under stringent conditions and a fibrous protein to a mammal.

15. (Withdrawn) A method for producing a cell-containing preparation, which comprises culturing a cell on the surface of a fibrous protein and transforming the cultured cells with a recombinant expression vector comprising a DNA having a base sequence represented by SEQ ID NO: 1 or 2, or with a recombinant expression vector comprising a DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 1 or 2 under stringent conditions.

16. (Withdrawn) A method for producing a cell-containing preparation, which comprises preparing a fibrous protein sheet by coating a fibrous protein onto a mesh sheet comprising a biodegradable resin; culturing a cell on the surface of the fibrous protein sheet obtained; and transforming the cultured cells with a recombinant expression vector comprising a DNA having a base sequence represented by SEQ ID NO: 1 or 2, or with a recombinant expression vector comprising a DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 1 or 2 under stringent conditions.

17. (Withdrawn) A method for producing a cell-containing preparation, which comprises transforming the cells with a recombinant expression vector comprising a DNA having a base sequence represented by SEQ ID NO: 1 or 2, or with a recombinant expression vector comprising a DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 1 or 2 under stringent conditions, and mixing the resulting transformant cells with a fibrous protein.

18. (Withdrawn) The method according to claim 14, wherein the cell is an epithelial cell of the oral mucosa, a skin cell or a fibroblast.

19. (Withdrawn) The method according to claim 14, wherein the fibrous protein is collagen.

20. (Withdrawn) The method according to claim 14, wherein the cells are deposited on the surface of the fibrous protein.

21. (Withdrawn) The method according to claim 14, wherein the cell is a transformant.

22. (Withdrawn) The method according to claim 21, wherein the transformant is transformed with a recombinant expression vector.

23. (Withdrawn) The method according to claim 22, wherein the recombinant expression vector is adeno-associated virus (AAV), retrovirus, poxvirus, herpes virus, herpes simplex virus, lentivirus (HIV), Sendai virus, Epstein-Barr virus (EBV), vaccinia virus, polio virus, sindbis virus, SV40 or plasmid.

24. (Withdrawn) The method according to claim 14, wherein the cell-containing preparation is capable of forming a peptide encoded by a DNA having a base sequence represented by SEQ ID NO: 1 or 2, or by a DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 1 or 2 under stringent conditions.

25. (Withdrawn) The method according to claim 14, wherein the cell-containing preparation further contains a mesh sheet comprising a biodegradable resin.

26. (Withdrawn) The method according to claim 25, wherein the biodegradable resin is polyglycolic acid.

27-29. (Cancelled)

30. (Currently Amended) A method for inhibiting growth, invasion and metastasis of cancer or for inhibiting angiogenesis, which comprises administering a cell-containing preparation comprising a cell which has a DNA having a base sequence represented by SEQ ID NO:2 or a DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO:2 under stringent conditions and encoding a protein which has an activity equivalent to NK4, ~~and~~ a fibrous protein and a mesh sheet comprising a biodegradable resin to a mammal, the cell being an epithelial cell of the oral mucosa or a fibroblast.

31. (Cancelled)

32. (Previously Presented) The method according to claim 30, wherein the fibrous protein is collagen.

33. (Previously Presented) The method according to claim 30, wherein the cells are deposited on the surface of the fibrous protein.

34. (Previously Presented) The method according to claim 30, wherein the cell is a transformant.

35. (Previously Presented) The method according to claim 34, wherein the transformant is transformed with a recombinant expression vector.

36. (Previously Presented) The method according to claim 35, wherein the recombinant expression vector is adeno-associated virus (AAV), retrovirus, poxvirus, herpes virus, herpes simplex virus, lentivirus (HIV), Sendai virus, Epstein-Barr virus (EBV), vaccinia virus, polio virus, sindbis virus, SV40 or plasmid.

37. (Previously Presented) The method according to claim 30, wherein the cell-containing preparation is capable of forming a peptide encoded by a DNA having a base sequence represented by SEQ ID NO:2, or by a DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO:2 under stringent conditions.

38. (Cancelled)

39. (Currently Amended) The method according to claim ~~38~~30, wherein the biodegradable resin is polyglycolic acid.

40. (Previously Presented) The method according to claim 30, wherein the cell is an epithelial cell of the oral mucosa, and is a transformant transformed with a recombinant expression adeno-associated virus (AAV) vector.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS AND AMENDMENTS

Claims 1-26 and 30-40 were pending in this application when last examined.

Claims 30-40 were examined on the merits and stand rejected.

Claims 1-26 were withdrawn as non-elected subject matter.

Claims 31 and 38 are cancelled without prejudice or disclaimer thereto. Applicants reserve the right to file a Continuation or Divisional Application on any cancelled subject matter.

Claims 30 and 39 are amended. Support for the amendment to claim 30 can be found throughout the specification as filed. It is noted that a skilled artisan would understand that the DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 2 as taught in the specification is functional. Claim 39 is amended to conform with the cancellation of claim 38.

No new matter has been added.

II. FOREIGN PRIORITY

The Examiner is respectfully requested to fully acknowledge the claim for foreign priority by checking boxes 12(a)(1, 2 or 3) on the coversheet of the next response.

III. INFORMATION DISCLOSURE STATEMENT

In item 1 on pages 2-3 of the Office Action, the Office indicated that references AL, AM and AO from the 1449 form of February 17, 2006, were not considered because of an absence of translation. Applicants note that translations of the relevant portions of these references were submitted with the IDS and 1449 form. For the convenience of the Examiner, the relevant portions of these references and another copy of these references are herein submitted. Furthermore, for the convenience of the Examiner, a copy of the 1449 form submitted is also provided.

IV. OBJECTIONS TO THE SPECIFICATION

On pages 3-4 of the Office Action, the specification was objected to for the noted reasons. Herein are amendments to the specification to alleviate these objections. It is further noted that support for the full meaning of the abbreviation "OMEC" can be found on lines 22-23 on page 18 of the specification.

No new matter has been added by these amendments to the specification.

V. ENABLEMENT REJECTION

On pages 4-9 of the Office Action, claims 30-40 were rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of inhibiting growth, invasion and metastasis of cancer or for inhibiting angiogenesis, which comprises administering a cell-containing preparation comprising a cell which has a DNA as set forth in SEQ ID NO:2, which encodes a mature human NK4 polypeptide, does not reasonably provide enablement for other fragments of variants thereof.

Applicants note that claim 30, the only independent claim, is amended to indicate that the hybridizable DNA encodes a protein which has an activity equivalent to NK4. Thus, Applicants suggest that a person of skill in the art could obtain such sequences by the hybridization methods disclosed in the application and determine if such sequences are active by methods also disclosed in the specification without undue experimentation. Thus, this rejection as applied to the amended claims, is untenable and should be withdrawn.

VI. OBVIOUSNESS REJECTIONS

On pages 10-13 of the Office Action, claims 30, 32, and 34-39 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Folkman et al. (US Patent 6,024,688) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T. (EP 1074264), Nakamura, T. (WO 99/55361) and Seki et al. (Biochem. Biophys. Res Commun. 172(1): 321-327, 1990).

Further, on pages 13-15, claim 33 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Folkman et al. (US Patent 6,024,688) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T. (EP 1074264), Nakamura, T. (WO 99/55361) and

Seki et al. (Biochem. Biophys. Res. Commun. 172(1): 321-327, 1990) as applied to claims 30, 32, and 34-39 above and further in view of Allen et al. (US Patent 7,115,256).

Finally, on pages 15-17, claims 31 and 40 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Folkman et al. (US Patent 6,024,688) in view of Kuba et al. (Cancer Res. 60(23): 6737-6743, Dec. 2000), Nakamura, T. (EP 1074264), Nakamura, T. (WO 99/55361) and Seki et al. (Biochem. Biophys. Res. Commun. 172(1): 321-327, 1990; hereafter Seki-A) as applied to claims 30, 32, and 34-29 above and further in view of Medico et al. (US Patent 6,551,991) and Junqueira et al. (Basic Histology, 1986, Lange Medical Publications, pp. 64-65).

Applicants respectfully traverse these rejections for the following reasons.

The method of amended claim 30 is characterized in that

(1) a cell-containing preparation comprises a cell, a fibrous protein and a mesh sheet comprising a biodegradable resin,

(2) the cell is an epithelial cell of the oral mucosa or a fibroblast, and

(3) the cell has a DNA having a base sequence represented by SEQ ID NO: 2 or a DNA hybridizable with a DNA having a base sequence represented by SEQ ID NO: 2 under stringent conditions and encoding a protein which has an activity equivalent to NK4.

Regarding characterization (1), the Examiner states that Folkman teaches combination with a therapeutic composition such as a matrix.

In particular, Folkman discloses in lines 6-18 on column 21 that angiostatin, angiostatin fragments, antiostatin antisera, angiostatin receptor agonists, or angiostatin receptor antagonists are combined with pharmaceutically acceptable excipients and optionally sustained-release compounds or compositions, such as biodegradable polymers. The biodegradable polymer of Folkman includes collagen (lines 19-28 on column 21).

As is clear from the disclosure above, Folkman teaches protein or a similar compound is combined with a biodegradable polymer such as collagen. On the other hand, in the cell-containing preparation of the invention, cells are combined with a fibrous protein.

In addition, the biodegradable polymer of Folkman serves as a sustained-release compound. On the other hand, as shown in lines 15-20 on page 21 of the specification, the fibrous protein of the present invention serves as a carrier of the cells. Containing the fibrous

protein permits the cell-containing preparation to be formed into various shapes such as a sheet, sphere and tube, and the preparation can be administered to all sites in the body.

Folkman neither teaches nor suggests that a fibrous protein is combined with cells so as to support cells in a desired site in the body.

The Examiner also states that Folkman teaches matrix made from biocompatible materials such as polyglycolide.

However, Folkman teaches polyglycolide as one of sustained-release compounds or compositions which sustainably release angiostatin or a similar compound (see lines 48-54 on column 11 and lines 19-26 on column 21).

On the other hand, the cell-containing preparation of the claimed invention includes a fibrous protein and a mesh sheet comprising a biodegradable resin. The mesh sheet maintains strength of the cell-containing preparation, although the fibrous protein comprises a culture medium suitable for culturing the cells. By including a culture medium in the fibrous protein, nutrients can be supplied to the cells in the cell-containing preparation, leading to stable and longer survival of the cells when the cell-preparation is administered to the living body (see lines 7-19 on page 22). In addition, the mesh sheet allows cells to be released in the opposite direction of the sheet, and cells can be efficiently delivered to the desired site of the living body (see figure 1 of the present application).

Folkman neither teaches nor suggests a cell-containing preparation comprising a mesh sheet as well as a fibrous protein to maintain strength of the cell-containing preparation, not only in the case where the fibrous protein does not comprise a culture medium but also in the case where the fibrous protein comprises a culture medium.

Regarding characterization (2) of claim 30, the Examiner states that Medico teaches that the most important target tissues of HGF are epithelia of different organs, such as liver, kidney, lung, breast, pancreas and stomach, and some cells of the hematopoietic and nervous systems and the presence of epithelial cells in the digestive track.

However, Medico merely suggests that epithelial cells can be target of HGF. In contrast, an epithelial cell of the oral mucosa of the invention is cell releasing NK4.

Using an epithelial cell of the oral mucosa in the cell-containing preparation of the present invention has the following advantages.

(i) Epithelial cells of the oral mucosa can be easily harvested without invasion into a patient such as an abdominal operation.

(ii) Since epithelial cells of the oral mucosa proliferate quickly, healing of the site of the oral cavity wherein epithelial cells are removed is accelerated.

(iii) Since epithelial cells of the oral mucosa proliferate quickly, harvest of a small amount of cells is sufficient for preparing cell-containing preparations.

(iv) Epithelial cells of the oral mucosa proliferate to form multilayered cells. Multilayered cells are unlikely to become extinct, thereby multilayered cells in the cell-containing preparation can release NK4 over a long period of time.

These advantages of cell-containing preparation comprising a fibrous protein and a mesh sheet and advantages of using an epithelial cell of the oral mucosa or a fibroblast are shown in declaration attached hereto.

Medico neither teaches nor suggests that an epithelial cell of the oral mucosa is used in releasing NK4, thereby provides the above mentioned advantages (i)-(iv).

Furthermore, the cells of the present invention include a fibroblast. Fibroblasts also form multilayered cells. Medico neither teaches nor suggests that a fibroblast is used in releasing NK4, thereby provides the above mentioned advantage.

Furthermore, other cited references neither teach nor suggest that an epithelial cell of the oral mucosa or a fibroblast is used in releasing NK4, thereby provides the above mentioned advantages.

As a result, the inventions of claim 30 and claims 32-37 and 39-40 depending on claim 30 are unobvious from cited references.

Thus, for the above-noted reasons, these rejections are untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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ATTACHMENTS

A. Copy of Form PTO-1449 submitted with IDS on February 17, 2006

B. Ref. AL – Mayumi, ""The Paradigm Shift of the Drug Concept - for disease treatment by large molecular medicines", Journal of Japanese Cosmetic Science Society Gakkai-Shi, Vol. 26, pp. 234-238, 2002. (with English translation of the 3rd, 9th and 10th paragraphs of the article)

C. Ref. AM - Ikada, "Overview", Protein, Nucleic Acid and Enzyme, Vol. 45, pp. 2139-2141, 2000. (with its English Translation)

D. Ref. AO - Yamaoka, "Molecular Designing of Biodegradable Polymer", Protein, Nucleic Acid and Enzyme, Vol. 45, pp. 2142-2149, 2000. (with English translation of the Abstract and Introduction on page 2142, Column 1 on page 2143, Column 4 on pages 2144-2145, and Conclusion on page 2148).

E. Declaration by Keigo Hanada